ID: O-OP-05

Segmentation of nucleus in HEp-2 specimen images using Fuzzy c-Means clustering approach

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Anti-Nuclear Antibodies(ANA) serves as a disease marker in the diagnosis of chronic autoimmune diseases. Indirect Immunofluorescence (IIF) in conjunction with Human Epithelial Type-2 (HEp-2) cells is considered as a hallmark in the diagnosis of these diseases. This process involves observing and categorizing the staining patterns of ANAs. Reliability of IIF based results are greatly affected by subjective factors and lead to inter and intra laboratory variability. Effective and consistent IIF image interpretation needs standardized and automated image processing algorithms. Segmentation of individual cell nucleus is highly essential to categorize the patterns. However, HEp-2 images are low contrast and may lead to incorrect pattern identification. In this work, an attempt has been made to segment the nucleus of the HEp-2 cells from twenty-eight subjects. The specimen images are obtained from a public domain database. Images considered in this study belong to six different staining patterns namely homogenous, fine speckle, centromere, nucleolar, coarse speckle and cytoplasmic. First, the images are subjected to pre-processing using Contrast Limited Adaptive Histogram Equalization (CLAHE) based contrast enhancement technique. Secondly, segmentation is performed on the pre-processed images to extract the nucleus using fuzzy c-means clustering approach. The evaluation metrics such as accuracy, sensitivity, true positive and dice metrics are used to validate the segmentation with the ground truth. The results show that the clustering based segmentation technique is able to segment the nucleus from the specimen images in all the six staining patterns. The segmented images are found to be in good agreement with the ground truth images with high correlation. It appears that the features can be extracted from the segmented images for the classification of the staining patterns. Thus, this study seems to be clinically useful and help in automated analysis of staining patterns.
Segmentation and analysis of brainstem in Alzheimer MR images using region based level set method

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Accurate segmentation of brain structures from MR images has been an open challenge mainly due to the absence of clear edges. Recent study on Alzheimer’s Disease (AD) have pointed towards brain stem to be the epicenter of the disease but few attempts have been made to decipher the effects of AD on brainstem structures. In this paper, an effort is made to segment brainstem and characterize it as a potential biomarker for detection of AD. A novel segmentation technique has been proposed to segment brainstem from the mid-sagittal view of the brain. The MR images which were used, are obtained from a public database containing 163 images from AD (CDR = 1) and non-AD (CDR = 0) classes. The MR images used for segmentation were preprocessed using skull-stripping and bilateral filtering. A distance regularized level-set evolution was implemented on the image to segment the brainstem structures. Along with improving the accuracy of segmentation, there has been an added focus on extracting features which could potentially help us classify AD from non-AD MR images. Features such as entropy, area and perimeter were processed using an SVM classifier and validated by a five-fold cross-validation. The brainstem was successfully segmented with an average accuracy of 96% (Pearson’s Correlation Coefficient), which is significantly higher than most standard techniques. The mean entropy, area and perimeter of the brainstems extracted from AD MR images were 8.8%, 8.3% and 9.6% lower than brainstems extracted from non-AD MR images, respectively. As this classification can lead to early detection of AD, this work could have clinical significance.
Investigation of regional pulmonary perfusion using Electrical Impedance Tomography

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Assessing the regional blood flow within the lung potentially helps to identify and treat pulmonary vascular diseases and might even support mechanical ventilation. Especially for guiding mechanical ventilation, bedside monitoring of both regional ventilation and pulmonary perfusion is desirable. Electrical Impedance Tomography (EIT) is a non-invasive imaging modality providing functional images of relative impedance changes induced by regional ventilation and blood volume changes, so-called cardiac induced impedance changes.

EIT data were acquired from human and swine lungs. The pulmonary perfusion was analyzed during different states of respiration: spontaneous breathing; mechanical ventilation and during respiratory hold phases. The EIT images were reconstructed using the Newton-Raphson algorithm. The cardiac induced impedance changes in the EIT images had to be separated from ventilation induced impedance changes. This separation was performed using methods from literature based on spectral filtering and statistical approaches. From the separated cardiac induced impedance component distributions of different features were derived and evaluated.

The perfusion parameters gained from EIT image reconstructions of swine lungs showed realistic blood volume flow distributions. Heart and lung regions could be distinguished. Validation based on lung perfusion reference modalities could be carried out. Options for reference imaging are Single Photon Emission Computed Tomography and Dual Energy Computed Tomography.

EIT could represent a technology for continuous lung perfusion monitoring. The EIT reconstruction images contain heart induced signal components, which can be used to compute perfusion dependent parameters. This additional monitoring information helps to optimize patient-specific lung-protective ventilation strategies. The physiological interpretation of the heart induced signals and the derived perfusion parameters should be further investigated in more detail based on simulation studies.
Design of complex RF pulse shapes for asymmetric excitation patterns via optimal control

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Introduction
Radio frequency (RF) pulses are used in magnetic resonance experiments to excite, invert and refocus magnetization. Computation of RF pulse shapes for a prescribed excitation profile is not trivial and therefore typically done by solving the simplified Bloch equation. Contrary to that, the presented design approach is based on the full time-dependent Bloch equations and allows a direct design of RF pulses that excite a specified target slice profile. While symmetric or antisymmetric magnetization patterns can be created with one component of the complex RF field, a fully arbitrary magnetization pattern requires both x- and y-components.

Theory
The efficient numerical solution of the optimal control problem is done by applying a Newton method which is embedded in a trust region framework using a matrix-free iterative solution of the Newton step. To achieve an accurate gradient information and application of the Hessian, the principles of adjoint calculus are used to compute exact derivatives by solving linearized equations forward and backward in time. The described approach is implemented in MATLAB and uses a constant trapezoidal slice selective gradient shape for the optimization of B1x and B1y.

Results and Discussion
The ability to control both components of the RF field simultaneously allows creating predefined arbitrary excitation patterns, e.g., simultaneous multislice pulses for three slices with different flip angles. The pulse shapes for both components are used to compute a complex RF shape, which is imported to a Siemens 3T Skyra MR scanner to validate the simulations with phantom and in-vivo experiments.

Conclusion
Typically, simultaneous multislice pulses are used to accelerate imaging experiments by an aliased acquisition of different slices with an identical flip angle. However, asymmetric excitation patterns with different flip angles could be used to accelerate quantitative parameter (e.g., T1 or T2) identification in multipulse experiments where each slice encodes a different temporal magnetization evolution.

Acknowledgement
Computer assisted assessment of bone metastases in the craniofacial skeleton including evaluation of CT-based versus CBCT-based application

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Within a research project about the inner structure of craniofacial bone, 3D-visualization of skeletal metastases was chosen as a special focus. As cone beam computer tomography (CBCT) is characterized by high resolution, good bone contrast, and less radiation compared to spiral computer tomography (CT), evaluation of CT-based versus CBCT-based application was included to the research.

For evaluation, a kind of envelope of the considered anatomical region, i.e. the mandibular condyle, was ipsi- and contralaterally segmented from CT-/CBCT-data. Bone metastases can be osteolytic, weakening the bone, and/or osteoblastic, linked to sclerotic processes. Based thereon, special transfer functions for slice oriented direct volume are defined, depending on whether CT or CBCT are evaluated. As detailed quantitative knowledge about Hounsfield values from CT is available, we there apply a physical color scale for graded display of the distribution of the gray values. For CBCT, we refer to two-tone visualization. The considered region is rendered in the foreground whereas the original anatomy is transparently displayed in black and white in the background.

The approach is demonstrated for metastases in a mandibular condyle due to Mamma-Carcinoma. Both, CT- and CBCT-based application provide precise display of localization and extent. Osteolytic processes in condylar head can be well differentiated. By ipsi-/contralateral comparison, affection of condylar neck is revealed. Quantitatively assessed, CT seems superior for evaluation of skeletal sclerosis. However, high resolution two-tone CBCT visualization displays detailed trabecular course which is nearly fully destroyed within the metastases.

With this approach, the physician can efficiently examine the lesion at several glances. CBCT-based visualization is rated as very suitable for evaluation of osteolytic lesions which are usually harder to be found by conventional diagnosis. With regard to reduced radiation dose of CBCT, these results can be of high benefit for patients who are subjected to frequent radiological imaging.
Combined Magnetic Particle and Magnetic Resonance Imaging of the Liver

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In vivo distribution of iron oxide based contrast agents developed for Magnetic Resonance Imaging (MRI) of liver lesions can be monitored with Magnetic Particle Imaging (MPI) since this method relies on the non-linear response of magnetic nanoparticles. In MPI the particles provide a positive contrast compared to negative contrast in MRI which is related to the T2/T2* relaxation process.

In this study the usability of MPI for liver visualizations and possible diagnostic as well as interventional applications is investigated and compared to MRI. Therefore, murine livers were labelled with iron oxide nanoparticles by intravenous injections of Resovist® (Bayer) with increased clinical doses (> 1 mg iron per kg body weight) at least four hours prior to the MPI measurements. The combined MPI-MRI measurements were performed on a 7T MRI (ClinScan, Bruker) and a preclinical MPI system (Bruker / Philips) according to an established workflow [1]. For reconstruction of the MPI measurement data and MPI-MRI image fusion a software framework based on the programming language Julia was used [2]. The measurement results show good correlation between MPI and MRI with noticeable mapping of the MPI-based particle distributions and the darkened liver on the T2 weighted MR images. Thus, MPI based liver visualization is feasible. Further efforts to prove MPI as diagnostic and interventional tool are under investigation.

Influence of Tracer Concentration on Image Reconstruction of a Commercial Preclinical MPI-Scanner

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Magnetic Particle Imaging (MPI) is a novel imaging modality being capable to resolve magnetic nanoparticle (MNP) distributions in biomedical applications with excellent temporal and spatial resolution. Two main reconstruction techniques are used to obtain the image of a spatial MNP tracer distribution in MPI: model based and calibration based. The latter, used in this contribution, estimates the tracer distribution solving an inverse problem combining a (measured) system matrix and a measurement. Since the inverse problem is ill-posed, additional knowledge has to be added to approximate a solution. Nevertheless, the MPI is believed to be capable to deliver quantitative results.

Resovist MNP at different concentrations were used as tracer to measure two system matrices and a tube phantom by MPI. The data were acquired on a Bruker pre-clinical MPI Scanner 25/20. Two system matrices using a small MNP sample (8 µL at 0.5 and 0.1 mol/l) were acquired with 100 averages, whereas the phantom measurements (pumping an MNP bolus of 0.2 mol/l through a tube of 1 mm diameter) were done without averaging. Images of the phantom were reconstructed with the two different system functions using a Tikhonov regularization scheme with a fixed parameter and a modified Kaczmarz algorithm. The images display strong differences depending on the system matrix used.

Thus, we studied the influence of the Tikhonov regularization by removing it and using a different reconstruction approach. This approach is truncate the system of equation based on the SNR of the measurement and the system matrix and approximate a solution using the same modified Kaczmarz algorithm. Again, similar results were obtained with a strong difference between the reconstructions of the phantom using different system matrices. Thus, to further localize the origin of the observed differences, a closer look at the physics behind the imaging process and the imaging device properties is required.
Possibilities of ultrasound measurements for in vitro differentiation of bone qualities D1-D4

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Pre-implant bone qualities influence the choice of implants, the surgical procedure, loading protocols and the prognosis of implant-supported prostheses. Currently, it is only possible to approximately determine bone densities preoperatively by using CT imaging. However, prior to uncomplicated surgical interventions three-dimensional diagnostics are often not performed as the additional radiation dose does not justify the information gain. It was the aim of this study to investigate the process of radiation-free quantitative ultrasound measurement (μUS) in preoperative evaluation of jawbone qualities and to verify the μUS measurements by micro-computed tomography (μCT) analysis.

57 bone cylinders (Ø 8 mm) were taken from Costae, mandibulae and maxillae of pigs and stored at 5 °C. All samples were subjected to μUS and μCT analysis. The ultrasound transmission velocity (UTG), bone mineral density (BMD), BV/TV (total against trabecular bone volume), and the visual inspection of several experienced examiners to differentiate D1 from D4 bone were compared. The correlation between μCT and μUS was quantified using a reference material. Ethical approval: The research related to animals use has been complied with all the relevant national regulations and institutional policies for the care and use of animals.

Both UTG and BMD (R = 0.483) as well as μUS and BV/TV (R = 0.437) showed good correlation. D4 bone is detected with a sensitivity of 74% and specificity of 74% at UTG<1700 m/s. D1 bone reaches a 75% sensitivity and 87% specificity at UTG>2000 m/s. The differences between D2 and D3 did not show statistical significance.

Using μCT scans to analyse the bone specimens for verification means of qUS measurements proved to be possible for the first time. The comparison of both methods shows that although the μUS measurement allows a radiation-free assessment of bone qualities, the accuracy of three-dimensional X-rays could not be achieved. In a next step intraoral measurements on patients will have to be performed. An enhanced μUS device might become a fast implantological diagnostic tool avoiding any radiation exposure.
Focusing ultrasound through anisotropic media

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Therapeutic ultrasound applications relying on coagulation (HIFU) or stimulation (LIFU) require the precise application of spatially confined acoustic energy. When it comes to brain disorders such as epilepsy or Parkinson’s disease, acoustic therapy/stimulation involves the application of acoustic fields through the skull. Due to its shape, the differences in acoustic impedance and speed of sound compared with the surrounding tissues, the skull leads to a reshaping of sound fields in comparison to fields in acoustically homogeneous tissues. Accordingly, precise and locally confined stimulation requires sophisticated methods for defining transmit delays.

We compared different methods for predicting accurate delays allowing to focus the acoustic waves on a defined location through acoustically anisotropic media.

A cranial bone geometry gained from a previously performed computed tomography scan was used as input data. For a given combination of array transducer position and focal point, the delays were calculated using a point source synthesis approach in consideration of the differences in thickness and geometry of the skull. As an alternative, ray tracing approaches were considered as well as FEM simulations. We investigated the level of simulation complexity that is required to achieve a reliable prediction of the delays which need to be used for accurate focussing through anisotropic media like the human skull. Furthermore, experimental methods relying on (optoacoustic) time reversal were investigated as well.

Experimental studies were performed on phantoms realistically mimicking relevant therapeutic settings in order to highlight the distortion effects resulting of the propagation through anisotropic media. In a second step, delays obtained from the numerical modelling were applied in order to demonstrate the potential of the different simulations for the correction of propagation effects and consequently for focusing through anisotropic media.
High-speed interleaved optoacoustic and plane wave compounded imaging

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Optoacoustic imaging combines high optical contrast with low acoustic scattering and extends optical imaging beyond the range of ballistic photons. Such as in any emerging modality, there is limited knowledge about the interpretation of optoacoustic data. For this reason, optoacoustic imaging is often combined with conventional ultrasound B-mode. However, most systems for “combined” US/OA imaging either work in optoacoustic or in ultrasound mode and a manual switching between the modalities is required. To overcome this limitation, we adapted our ultrafast ultrasound system (latest generation of DiPhAS – Digital Phased Array System, Fraunhofer IBMT) so that it enables an interleaved US/OA mode. In our high-speed system, the frame rate is only limited by the PRF of the laser system in optoacoustic mode. The system itself does only acquire channel data that are processed in a GPU. Data from 128 channels are digitized with 80 MSamples/s. Currently, the base clock of the system is set to 100 Hz, which corresponds to the PRF of the integrated laser system (customized version of NT232, EKSPLA). The 10 ms between two trigger signals are used for one optoacoustic frame and multiple ultrasound plane wave acquisitions, whose number depends on the image depth (and the corresponding data amount) and the acoustic time of flight as an ultimate limit. The system was evaluated in both modalities with different linear array transducers in the frequency range from 5 to 10 MHz. The imaging performance was assessed on commercial phantoms for the ultrasound mode and on custom made wire phantoms for the optoacoustic mode. Further, hybrid US/OA data from subcutaneous vasculature were acquired from human probands. With its high frame rate capabilities, the system provides the technical prerequisites for imaging highly dynamic processes simultaneously in optoacoustic and ultrasound mode.
Shear wave elastography is a relatively recent technology aiming at extracting information concerning the stiffness of soft body tissue. This information can be very useful when it comes to diagnosing potentially carcinogenic body tissue, as stiffer tissue parts are more likely to be pathological than softer tissue parts. Shear wave elastography is based on a focused ultrasound beam in the examined tissue. The disturbance created by this focused beam travels orthogonally to the axis of the focal point through certain soft tissue (e.g. liver tissue) as a shear wave. New ultrasound imaging technologies, like ultrafast imaging, allow for the measurement of the propagation of those shear waves by imaging the induced displacements in the tissue. In this work, we extracted the shear wave speed (SWS) from simulated and experimental ultrasound signals as this SWS can be used to deduce quantitative stiffness information of tissue. In order to achieve this goal, several virtual and real experiments were performed and different approaches for measuring the SWS were implemented in MATLAB. The shear wave propagation simulations in soft tissue were performed in Field II. For experimental measurements, the “Digital Phased Array System” (DiPhAS) ultrasound research platform, developed by IBMT, was used as this system is capable of acquiring data sets at kHz rates. Different methods for extracting SWS and tissue stiffness parameters were applied to synthetic and experimental data in order to assess the accuracy of our algorithms.
Analysis of corneal subbasal nerve fiber length in mosaic image series acquired by guided eye movements

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A recently proposed technique enables the generation of continuously increasing mosaic images of the corneal subbasal nerve plexus (SNP) using in vivo corneal confocal microscopy (CCM). The aim of the present study was to investigate the progression of the corneal nerve fiber length (CNFL) measured in the growing mosaic images with regard to the increasing recorded area. Five large data sets that had been previously recorded from three healthy volunteers using the proposed CCM technique were included in the study. Intermediate mosaic images were created from successively growing partial data sets and assessed for CNFL. The measured CNFL progression shows both over- and underestimation and high variability of the CNFL for small observed areas. The relative deviation of means from values of two independent CCM examinations of two of the subjects reveals high differences for an observed area of <1.5 mm². Increasing the mosaic image area stabilizes the CNFL values and reduces both the moving variance (MV) as well as the intra-patient deviation in all datasets. The two provided measures quantify different area-dependent aspects of the CNFL measured in an expanding mosaic image. The MV measures how stable the CNFL can be considered at a certain mosaic size. The relative deviation of means from two repeated CCM examinations on the other hand provides some indication on the level of reliability that can be expected from the measured CNFL. The progression of CNFL in the examined datasets manifests a potentially very high variability for mosaic sizes of less than about 1.5 mm². Above that size, CNFL progression and the intra-patient relative deviations both stabilize significantly in all five datasets. The results of the present examination suggest a recommendation for a minimum sampled area of the central SNP of 1.5 mm² for reliable and meaningful measurement of CNFL.
ID: O-OP-20

Mapping of Functional Integrity of Brain Cortex in Glioma Patients by Intraoperative Optical Imaging using Direct Cortical Stimulation

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Brain tumor resection is even with today’s modern imaging modalities one of the most challenging disciplines in neurosurgery. With the progression free survival time of the patient being related to the extent of resection, the neurosurgeon faces a trade-off between maximizing the degree of tumor resection and the risk of postoperative functional deficits. Intraoperative Optical Imaging (IOI) recently demonstrated its potential as a tool for localization of functional brain areas, such as the sensory or visual cortex. Here, we present a new IOI application for the intraoperative distinction of tumor and normal brain tissue. Therefore, IOI was combined with direct cortical stimulation (DCS). Measurements were intraoperatively performed on patients that underwent resection of superficial low-grade gliomas. The exposed cortical surface of each patient was directly electrically stimulated on multiple stimulation sites while simultaneously images of the cortical surface were acquired with a camera attached to the surgical microscope. Each electrode position of each stimulation site was classified in regard to stimulation of non-tumor or tumor tissue based on MRI data and whitelight images acquired after tumor resection. From each electrode position a time course, representing changes in the optical properties of the cortex induced by direct cortical stimulation, was extracted. A dynamic linear model was used to model the reflectance change induced by stimulation and to correct for heartbeat and respiration artifacts. Various features of the calculated reflectance time course models were compared to identify differences of non-tumor brain tissue and tumor tissue, respectively. The results reveal significant differences in model features, e.g. a higher maximum decrease in cortex reflectance on non-tumor stimulation sites. The results are giving first evidence that the method could be a useful tool for defining the resection borders during brain tumor surgery.
Local binary patterns for differentiation of brain tissue types
in optical coherence tomography images

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Since the beginning of the 1990’s Optical Coherence Tomography (OCT) has been established as a powerful technique for biomedical imaging. The first commercial application was in ophthalmology, followed by dermatology. OCT is a non-invasive imaging modality with a typical resolution of 1-15 µm and a penetration depth of 1-2 mm. Due to these characteristics it has found its application in many research areas. The objective of our research is to investigate the potential of OCT to support neurosurgery by distinguishing different types of brain tissue which is a critical but essential challenge. In a study we measured ten ex vivo brain tissue samples with a commercially available Thorlabs Callisto OCT system. Eight of them were benign brain tumor samples (meningioma) and the two remaining samples contained healthy gray and white brain tissue. On the acquired three dimensional images a number of post processing steps were performed. First a median filter was applied to suppress noise. Afterwards, for each B-Scan of the 3D data set, the region of interest was segmented and then divided into 32x32 subimages. On these subimages a texture operator based on local binary patterns was applied and histograms were calculated. The dimensionality of these histograms was reduced by employing principal component analysis. Then a classification was done using a support vector machine with a radial basis kernel function. A grid search was performed to find the optimized parameters. Moreover a 10 fold cross validation was done to verify our results. The efficacy of our approach was greater than 98% for the differentiation between the three tissue types. With these findings we can conclude that OCT in combination with local binary patterns is suitable to support neurosurgeries. In the future we will confirm this outcome by in vivo measurements.
Motion Artifact Removal in Optical Mapping of Cardiac Tissue

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Optical mapping is a widely used fluorescence imaging technique used in biomedical research for studying electrical wave propagation in the heart. The technique is capable of visualizing wave phenomena across macroscopic areas of the cardiac muscle with millisecond temporal and at millimeter to micrometer spatial resolutions. This resolution makes it a gold-standard technique for characterizing wave phenomena associated with different cardiac arrhythmias such as ventricular fibrillation. While the technique provides highly detailed visualizations of the behavior of, for instance, transmembrane voltage or intracellular calcium concentration, one of its major shortcomings is its sensitivity to motion artifacts. Motion artifacts can significantly distort the fluorescent signal and prohibit extraction of the measured parameters overall. Motion artifacts may be effectively suppressed using pharmacological uncoupling. However, we demonstrate that motion artifacts can also be significantly reduced using computer vision techniques. We show that image registration of the optical mapping data may result in stabilized image sequences with no visible motion. Motion artifacts arise due to relative motion of the camera sensor and the moving tissue. Conventional signal processing techniques used in the post-processing of optical mapping data enhances motion artifacts. Here, we present algorithms to characterize and inhibit motion artifacts observed in experimental video data and in synthetically generated optical mapping video data using electromechanical simulations. We show that motion artifacts can be significantly reduced such that in certain conditions the use of uncoupling substances becomes obsolete.
Determination of needle axis in in-plane acquired 3-D ultrasound image volumes using stick transform

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Tracking surgical instruments in image guided, minimally invasive interventions is an important task to increase the success of the procedure. Ultrasound is a non-ionizing imaging modality with real-time capabilities, which makes ultrasound attractive for monitoring instrument positions in minimally invasive interventions like core biopsies. On the other hand, highly echogenic objects like biopsy needles generate complex artifacts in ultrasound images, and thus impede to intuitively determine the position of the needle tip.

Several approaches to enhance linear structures in medical images have been proposed like multiscale vessel enhancement filtering or 2-D filtering with “sticks”. We adopted this idea – called stick transform in the following – for use in 3-D data.

A total of 44 ultrasound volumes has been acquired via the Art.Lab interface of a MyLab 70 ultrasound system (Esaote Europe B.V., The Netherlands) connected to a mechanical 3-D probe (BL433). The raw data – summed A-lines – contain the reflection signals of a 16 G (diameter = 1.29 mm) needle pushed into pork liver, which have varying azimuthal (φ) and polar (θ) needle orientation relative to the image planes. Sampling frequency of ultrasound raw data was 50 MHz, image reconstruction mainly consisted of Hilbert transform and logarithmic compression, and image volumes of cubic voxels (0.245 mm × 0.245 mm × 0.245 mm) were generated.

$R \times R \times R$ image sub-volumes were correlated with equally sized binary templates of sticks with defined discrete stick orientation $(\phi, \theta)_{\text{discrete}}$. Such, each image sub-volume was assigned to an optimal fitting angle pair $(\phi, \theta)_{\text{opt}}$. Voxels then were classified by identical $(\phi, \theta)_{\text{opt}}$. The voxels of the largest class were approximated by a straight line using LS minimization. In addition, an expert defined the $(\phi, \theta)_{\text{expert}}$ ($\phi_{\text{expert}} \approx 90^\circ$ due to in plane technique) for the needles.

Best coincidence of automatically $(\phi, \theta)_{\text{opt}}$ and expert defined $(\phi, \theta)_{\text{expert}}$ needle axes was achieved for $R=10 \times \text{diameter}$ with 97%-quantiles misalignments $\Delta \phi = |\phi_{\text{opt}} - \phi_{\text{expert}}| < 4^\circ$ and $\Delta \theta = |\theta_{\text{opt}} - \theta_{\text{expert}}| < 4^\circ$. 

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Download Date | 8/30/18 10:43 PM
Development of Patient-Specific TAVR to Reduce Regurgitation

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Introduction
With a total of more than 10,000 operations in 2014 in Germany, transcatheter aortic valve replacement (TAVR) has become an established and widespread technique for treating severe aortic valve stenosis. However, patient-specific factors, in particular the severity and pattern of aortic valve calcification, can result in complications, such as paravalvular leakage, when using TAVR, which in turn can adversely effect long-term patient prognosis. Preoperative simulation of a TAVR provides vital information for the selection of the appropriate valve therapy (interventional vs conventional).

Methods
Numerical simulation models combine patient-specific vascular anatomy with bi-directional Fluid Structure Interaction (FSI). The patients’ thoracic arteries, including calcification deposits, are preoperatively captured using CT/MRT. Mimics® Innovation Suite was used for both segmentation and CAD editing. A 3D CAD model was generated by reverse engineering a biological aortic valve (porcine/bovine leaflets). Solvers, Fluent®, and Mechanical® (ANSYS®), were used to simulate flow inside the aortic model under two sets of material properties: linear elastic and hyperelastic.

Results
The simulation model was used to compute flow-induced leaflet movement in a biological model. The CFD Fluent® solver plotted major changes in the fluid mesh and high quality flow computations. Velocity traces for the two aortic models, linearly elastic and hyperelastic, were almost identical except at the peaks and troughs. Likewise, the development of shear stresses in both material property sets was similar. The aorta behaved linearly elastic at pressures in excess of 80 mmHg; at pressures lower than 80 mmHg, the hyperelastic model more closely approximated reality.

Conclusion
This study vindicates the workflow used for the acquisition of patient-specific anatomy and bi-directional FSI simulation. The next step entails positioning the biological valve in the virtual, individualized anatomy before the FSI simulation to detect and reduce possible paravalvular leakage.
Selective Visualization of Mammary Ducts of sub-millimeter diameter in 3-D Ultrasound Image Volumes

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The topographical ductal anatomy of the breast is relevant for diagnostic and therapeutic reasons. Breast diagnostics is often directed to the detection of suspicious lesions having diameters in the range of millimeters. Malignancies can develop from precancerous malformations, which most frequent entities are ductal carcinoma in situ (DCIS). Those are originated in the ductal epithelium. A breast conserving therapy addresses a resection of a minimum of lobe tissue. The affected tissue can be identified in relation to the topographical ductal anatomy of the breast. Therefore, it seems adjuvant to detect mammary ducts. Galactography is a common radiographic and technical demanding interventional technique to demonstrate selected ducts. Alternatively, highly resolved ultrasound volumes could potentially help to get deeper insight to the anatomical relations.

Six volume data sets – approx. 720 × 560 × 320 voxels, resolution 0.07 mm × 0.21 mm × 0.52 mm (axial × lateral × elevational) – were acquired using an ACUSON S2000 Automated Breast Volume Scanner (ABVS) ultrasound system (Siemens Healthcare). They show the mammary ducts and lobuli down to lobuli glandulae mammariae even in the non-lactating breast, blood vessels, cooper ligaments, and fatty tissue. Due to the limited resolution in elevational direction, terminal ductal lobular units (TDLUs) are only visible occasionally, i.e. when mainly oriented along the axial-lateral plane.

The following procedure was implemented: The user interactively identifies two distant voxels along a mammary duct. It is visualized by direct volume rendering with voxel’s gray scale-dependent opacity alternatively as a (1) straight line, as the (2) shortest path weighted by the voxel’s gray scale values or as the (3) shortest path weighted by structureness parameter from Frangi’s multiscale vessel enhancement filtering. Additionally, the enclosed tissue is visualized with viewing axis along and orthogonal to the mammary duct to demonstrate TDLUs.

Shortest paths (2, 3) did show the highest coincidence with expert determined mammary ducts, and structureness parameter weighting (3) could close small gaps in the duct. Viewing axis orthogonal to the mammary ducts could visualize the topographical relation of TDLUs to mammary ducts more clearly, due to the limited elevational resolution.
ID: O-OP-31

Advanced Analysis of Tracers for Magnetic Particle Imaging: Magnetic and Geometric Characterization by Multidetector Field-Flow Fractionation

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Magnetic nanoparticles (MNP) exhibit unique magnetic properties making them ideally suited for a variety of therapeutic (e.g. hyperthermia and targeted drug delivery) and diagnostic (e.g. magnetic resonance imaging and magnetic particle imaging) biomedical applications. Depending on the particular scope MNP must thereby meet special magnetic requirements which are closely related to their structural properties (e.g. size distribution). Furthermore, it is really challenging to prepare MNP with lowest size and shape dispersion making a reliable size determination difficult due to limitations of common size measurement methods (e.g. dynamic light scattering, DLS). Chromatographic separation techniques, such as asymmetric flow field-flow fractionation (A4F), coupled with complementary detectors provide a powerful approach for size fractionated multidimensional analysis of MNP. We have recently introduced Magnetic Particle Spectroscopy (MPS) as a novel online detector capable to magnetically quantify and characterize MNP under commonly applied A4F conditions. We successfully integrated MPS into an A4F multi-detector platform including DLS, multi-angle laser light scattering as well as ultraviolet detection and investigated the commercial MRI contrast agents Resovist®, Endorem®, and Feraheme®. Compared to results of common batch mode measurements our A4F measurements revealed a complex size distribution with two distinct populations for Resovist®, and continuous broad distributions for Endorem® and Feraheme®. Furthermore, we found by online MPS that the magnetically characteristic signature of the MNP was strongly affected by the hydrodynamic splitting appearing in a nonlinear dependence of MPS spectra (e.g. amplitude, harmonic ratio) on size.

A novel method for separation and quantitative magnetic characterization was developed by coupling MPS with A4F. It turns out that online MPS method serves as an attractive extension of separation based MNP characterization.
Interactions of Protein Corona Coated Magnetic Nanoparticles and Human Cells

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When magnetic nanoparticles (MNP) are exposed to the blood circulation, a protein corona is formed immediately on particles surface. The composition of the protein corona might be of major importance for cellular uptake. Therefore, the aim of our study was to analyze corona formation during in vitro serum incubation depending on the composition of the protein source and to investigate the interactions of these particles with living cells.

For the formation of the corona we incubated cytotoxic polyethylenimine (PEI) coated nanoparticles in defined mixtures of cell medium and fetal calf serum (FCS) for defined times and temperatures. Before and after the incubation the physical properties of the MNP were determined (zeta-potential, vibrating sample magnetometry, magnetorelaxometry, thermogravimetric analysis, transmission electron microscopy as well as sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)). Effects on cell viability were investigated for human brain microvascular endothelial cells (HBMEC) by the CellTiter Glo™ test and for long-term viability by real time cell analysis (RTCA). Particle–cell interactions with HBMEC were investigated by means of flow cytometry of fluorochrome-labelled particles.

Since the zeta potential of incubated MNP varies as a function of FCS concentration, its influence on the formation of the protein corona is clearly demonstrated. This effect was confirmed by SDS-PAGE and thermogravimetry. Magnetorelaxometry revealed that corona formation takes place within seconds. No cytotoxic effect of PEI-coated MNP was observed after protein corona formation. Similarly, long-term viability assays (RTCA) showed that the protein corona masks cytotoxic effects. Additionally, flow cytometry indicated that FCS coating reduces the particle–cell interaction of cytotoxic PEI-coated MNP.

Here we present a promising novel type of biocompatible magnetic core-shell nanoparticles for application in medicine. Ongoing investigations focus on corona formation kinetics and in vitro and in vivo experiments on the biological fate of serum incubated MNP after cellular uptake.

This work is supported by Deutsche Forschungsgemeinschaft (DFG) in frame of priority programme 1681 (FKZ: CL202/3-2, DU 1293/4-2, LU800/4-2, SCHA1640/7-1).
ID: O-OP-34

Setup of a sleep recording system compatible with magnetoencephalography

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The study of sleep disorders is best done in a clinical sleep laboratory by polysomnography (PSG), which allows to record all physiological signals necessary to determine sleep macrostructure (sleep stages), sleep microstructure (arousal), as well as related behavior of cardio-respiratory parameters. Typical signals include electro-encephalography (EEG), electromyography (EMG), thorax and abdomen respiration movements, nasal air flow, electrocardiography (ECG), oxygen saturation, and time synchronized video. To perform studies of PSG signals in parallel with magnetoencephalography (MEG) is difficult. A MEG laboratory consists of a magnetically shielded room (MSR) as MEG requires very low ambient magnetic fields in the range of pT. Here we describe a setup of PSG which is compatible with MEG. Recording of electrical signals is often available in MEG and some of the EEG channels were used for ECG recording by using voltage dividers to avoid saturation. Bipolar electrical inputs were used for EMG. Custom made piezo sensors for thoraco-abdominal movement recording and a commercial thermocouple for nasal air flow allowed recording of these respiratory signals through available electrical inputs as both piezo crystals and thermocouples generate small voltages. For oxygen saturation measurements we assessed a commercial device developed for magnetic resonance tomography. It did not disturb the MEG recording and its output was recorded synchronously with the other signals. The recorded signals were stored in the EDF+ format and imported into clinical PSG scoring software for offline sleep analysis. Pilot data verified the operability of this PSG setup without interfering with the MEG. Future work will study the feasibility of sleep stage analysis with this PSG setup.
Magnetorelaxometry tomography for quantitative imaging of the mobility of magnetic nanoparticles

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Magnetic nanoparticles (MNPs) are applied as drug carriers or heat generators in novel cancer treatment approaches. For these applications a quantitative imaging of the MNP distribution inside a body is essential. Furthermore, since the MNPs are acting on a cellular level, an imaging taking into account their mobility within the biological matrix would be extremely advantageous.

Magnetorelaxometry (MRX) tomography is based on the magnetic moment relaxation of MNPs after switching-off an external magnetic field. Thereby, the mobility of the MNPs partly determines the relaxation. At present, the image of a MNP distribution is reconstructed from sequential MRX measurements using varying magnetic field patterns for spatially encoded relaxation signals.

We extended MRX tomography by including information about the influence of the MNP mobility on the relaxation into the reconstruction. In a first setup we used two different mobility states of MNPs, fluid (Brownian and Néel relaxation) and immobilized (merely Néel relaxation). For the measurements we assembled a suspension of fluid MNPs and 9 MNP loaded cubes \((l=12\text{mm})\) of MNP immobilized in gypsum inside a mount \((10\times10\times6\text{cm}^3)\). Magnetic field patterns were sequentially generated for 1s by 30 planar excitation coils \((d=36\text{mm})\) and relaxation signals were detected by the PTB 304 SQUID magnetometer.

We could reconstruct MNP distributions for bound and unbound MNPs with a resolution in the milligram per cm\(^3\) range and a total deviation of MNP amount of less than 10% within a field of view of 240 cm\(^3\). We conclude that MRX tomography provides a quantitative imaging of the spatial distribution and mobility of MNPs over volumes larger than 100 cm\(^3\). Thus, MRX tomography might become a valuable tool in MNP-assisted cancer therapies allowing quantitatively imaging the MNP mobility.
High Frequency Ultrasonic Transducers Using Soft Mold Process

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High resolution imaging requires high frequency ultrasonic transducers. For fabrication, fine scale 1-3 piezocomposites are necessary. Due to the brittleness of the ceramic, the limited blade width and the increasing effort, conventional dice-and-fill technique becomes increasingly insufficient as pillar size and kerf become smaller. The soft mold process offers the fabrication of fine scale piezoceramic arrays with free design of ceramic pillars. The basis of this approach are master molds, which are structured by microsystems technologies like LIGA, SU8 and deep reactive ion etching (DRIE). That allows a high variety of rod size, shape, spacing, and arrangement. The combination of silicon industry based microstructuring and ceramic molding is possible through soft plastic templates taken from the master mold, which are reusable. A ceramic slurry based on a piezoceramic material is filled into the soft molds under vacuum and therein dried. After demolding, array structures are debinded, sintered and filled with an epoxy polymer. Ceramic body and excessive epoxy are removed by grinding and the resulting 1-3 piezocomposite lapped to the desired thickness, electroded and poled.

In this contribution, we report on the development of a 20 MHz ultrasonic transducer based on round piezoceramic pillars in hexagonal arrangement with sintered dimensions of 34 µm diameter, 160 µm height and 10 µm spacing. 1-3 piezocomposites made of these structures show coupling coefficients $k_t = 0.6$. Phased array ultrasonic probes have been manufactured by selection of appropriate backing and matching layers. The composition of the matching layers was adjusted to the acoustical impedance of water and grinded down in order to meet quarter wavelength criteria. For characterization of acoustic properties, pulse-echo curves and sound field intensity plots have been measured. Experimental results will be presented in detail and will be compared to modelled data.
3D Ultrasound Tomography for Breast Cancer Diagnosis

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A promising candidate for sensitive imaging of breast cancer is 3D ultrasound computer tomography (3D USCT). The main advantages of USCT are simultaneous recording of reflection, attenuation and speed of sound images, high image quality and fast data acquisition. Due to the defined patient positioning and no breast deformation, the volume images of the female breast are reproducible. Building such a device for clinical practice was not successful for a long time - mostly due to the huge data rate and the time-consuming image reconstruction. Currently, the first 2D systems have become available for clinical evaluation. At KIT we developed and tested the first full 3D USCT system. The 3D USCT device is equipped with 2041 ultrasound transducers with 2.5 MHz center frequency and 50% bandwidth. The data acquisition is carried out by sequentially selecting a single emitter, sending a frequency coded chirp and recording the transmitted and reflected waves with all receivers. Rotational and translational movement of the aperture is applied to enhance the image contrast. Up to 40 GB of raw data is digitized with 480 parallel channels at 12 Bit and 20 MHz sampling frequency. A 3D synthetic aperture focusing technique (SAFT) is applied for reflectivity image reconstruction, which is highly compute-intensive. Sound speed and attenuation images are reconstructed using a straight ray based algebraic reconstruction technique. Parallel reconstruction on GPUs enables high resolution breast volumes in 40 minutes. In a first pilot study ten patients with different lesions were imaged. Speed of sound, attenuation and reflection images of each patient were derived from the raw data. Overlaid volumes of the modalities show qualitative and quantitative information at a glance. The results are promising as the breasts' tissue structures and cancerous lesions could be identified in the USCT images. A larger clinical study was started recently.
Detection and tracking of microbubbles for vascular imaging in oncology

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Ultrasound imaging is a promising modality for molecular and vascular imaging in oncology using microbubbles as contrast agents. These microbubbles are clinically approved, have diameters of typically 1-2µm so that they can pass the smallest capillaries and provide sufficient contrast for single microbubble detection in ultrasound imaging. As resolution of ultrasound imaging is in the order of 100µm-500µm microbubbles close to each other cannot be resolved. However, when single microbubbles pass the capillaries they can be detected and localized with an accuracy much higher than the imaging resolution. Tracking the microbubble positions allows to generate super-resolution images of the vasculature together with flow velocities. Flow velocities below 1 mm/s can be measured, which is much lower than the velocities that can be measured by Doppler ultrasound.

With dense flow patterns and up to hundreds of microbubbles detected in a single frame of a video sequence, tracking microbubbles becomes a complex combinatorial task that we address using multiple target tracking algorithms as Multiple Hypothesis Testing and Markov Chain Monte Carlo Data Association. We demonstrated the reliability of the algorithm in simulations, phantom measurements and in vivo measurement of different tumor xenografts. The results of the simulation and phantom studies demonstrate the ability to measure flow velocities of 1mm/s and below. The resolution achieved is about 10 times higher than the imaging resolution. Results of super-resolution in in-vivo images of murine tumor xenografts are presented for different tumors. They show the potential of the method to image small capillaries with super-resolution and characterize the tumor types and their aggressiveness by their different vessel morphology and flow characteristics.
Self-adapting autofocus function for intravital microscopy using a tunable liquid lens

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The visualization of dynamic processes of biological samples is a challenging task. One example with high clinical interest is the visualization of alveolar structures in lung tissue during uninterrupted mechanical ventilation. Imaging these processes in animal models like rats supports the understanding how different ventilation parameters affect the sensitive alveoli and improve the knowledge about protecting lung tissue during longterm ventilation treatments. By using a video camera with high magnification, a sample movement in axial direction often causes a loss of focal plane. Therefore, the camera focus has to be adjusted to track the sample movement properly. In this study, we present a custom-made self-adapting algorithm using a tunable liquid focus lens. The focus of this lens can be shifted by using an electroactuator whose effective current is adjustet via an USB lens driver connected to the PC. The focus value is estimated from the video image using edge detection. Because each sample moves a little bit different and movement characteristics change with frequency and amplitude which simulates different ventilation parameters (e.g. ventilation rate and ventilation volume), the focus lense cannot be driven with a fixed set of current values to keep the sample in focus. Therefore, our self-adapting algorithm uses an array of 100 current values for the whole periode and adjusts these values over several cycles by comparing focus values extracted from the video images to decide which value has to be increased or decreased to fit the sample movement.

With this setup, we are able to visualize the movement of a mechanically ventilated lung phantom over the distance of one millimeter in axial direction, which is in the same range of real lung tissue movement, whereat the adjustment takes just a few ventilation cycles.
Tissue stiffness of trabecular bone does not change in patients with atraumatic vertebral fractures

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Areal bone mineral density (aBMD), measured by dual energy x-ray absorptiometry (DXA), is the clinical gold standard to assess bone status. The aim of this ongoing study is to elucidate the question to which extend a decrease of spinal aBMD is caused by a decrease in bone volume or decree of mineralization of bone (DMB). DMB is indirectly reflected by the acoustic impedance measured with scanning acoustic microscopy (SAM), which was performed on half-cylindrical trabecular bone biopsies obtained during kyphoplasty surgery of 32 patients with atraumatic vertebral fracture (Fx) and posterior lumbar interbody fusion (PLIF) surgery of 30 patients with spinal degenerations (Ko). The biopsies had been embedded in PMMA for histomorphometric analysis and were polished to avoid artificial signal decrease caused by surface roughness. The confocal reflection amplitude was measured by scanning a 100-MHz focusing transducer over the sample. The matrix stiffness was estimated using a defocus correction and calibrated using homogeneous reference materials. The 95th percentile of the stiffness distribution was determined to evaluate potential differences between the two groups and a normalized elasticity distribution function was generated for each sample. These functions were then averaged for each group. No significant differences were found between the Fx and Ko groups (p=0.887). The shapes of the averaged functions were also similar, suggesting that tissue elasticity at the microscale does not differ between the two groups. This study will later be complemented by 3D histomorphometric data from micro-computed tomography (μCT) scans, aBMD of the lumbar spine by DXA and volumetric BMD (vBMD) and structural analysis results of clinical pQCT of selected vertebrae. In summary, these preliminary findings indicate, that reduced compressional strength of vertebrae is not due to a decrease in tissue elasticity, but likely to be dominated by differences in bone volume and trabecular architecture.
Transfer characteristics of iterative reconstruction techniques

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The institute for biomedical engineering and informatics at the Ilmenau University of Technology holds an experimental computer tomograph. It is an inverse third generation where the object and not the tube-detector assembly is rotated. Since 2000 the reconstructions are done with the filtered backprojection and since 2013 an iterative reconstruction technique can be used. The main goal of the iterative technique is the reduction of radiation dose and a constant or even improved image quality at the same time. In general, the iterative reconstruction method compares synthetic projection data with the original projections and corrects the previously reconstructed image. We compared the resulting images from the filtered backprojection and from the iterative reconstruction and examined the imaging properties of the system with the two reconstruction methods. For the examination a specific phantom for computer tomograph evaluations was used. The phantom allows for the evaluation of the resolution by a PMMA-air pattern (0.3 mm – 1.0 mm), metal artefact examination, modulation transfer function calculation and the evaluation of Hounsfield units. Using this phantom, the iterative reconstructions show a significantly better image quality, especially in terms of resolution, contrast to noise ratio and signal to noise ratio. Even a low dose acquisition (100 kV, 1.5 mA, 0.05 ms integration time) results in better image quality using the iterative reconstruction method compared to the filtered back projection. By adjusting the integration time, we examined four different doses at 25%, 50%, 75% and 100% of the full dose (100 kV, 1.5 mA, 0.2 ms integration time per projection). The only disadvantage of the iterative methods is the increase of the reconstruction time, which depends on the number of iterations. We could show in this study how the iterative reconstruction methods significantly improve the image quality while decreasing the radiation dose even at 25% of the full dose.
High-throughput 3D volume measurement of polymer rods
Design and implementation of a solution for a high-precision volume measurement of polymer rods with optical measuring technique and subsequent imaging processing

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Small polymer rods (diameter = (150 – 700) µm, length = (0.7 – 8) mm, weight = (30 – 120) µg) are produced for pharmaceutical applications. For quality assurance-reasons the target weight has to be checked. A high-precision, low throughput weighing instrument is presently used. For the next generation of polymers, the product dimensions are supposed to be further reduced while keeping the production tolerances constant. The latter is in conflict with present state-of-the-art weighing technology since the min weight specification will be violated. Since the density variation is known to be negligible an alternative approach is to determine the volume of the polymer rods. The cross sections of the polymer rods are approximately circular. Due to the production of the fragments it cannot be assumed that the abutting faces are orthogonal to the symmetry axis of the polymer rod. Therefore it has to be analyzed what the impact of small deviations from circular cross-sections as well as the non-ideal abutting faces is. Based on the current state-of-the-art technology the following methods are discussed: the sheet-of-light technique, computer tomography or the depth-from-focus method. The advantage of all three methods is the non-contact, non-destructive measurement. Our new concept combines the advantages of the mentioned methods: it is invariant to color/brightness changes and pictures can be taken in any number. In addition the recording and evaluation are considerably faster. The polymer is observed by a camera in transmitted light. Therefore the diameter and the length are visible. The object is rotated around to the longitudinal axis by means of a mechanical fixture. Thus pictures of all sides can be recorded. The diameter and the length are calculated with the image processing. The approach is very promising. The uncertainty of the system will be characterized in the next steps.
Virtual Template Registration – a general approach to control motion in DCE-MRI

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Introduction
Registration of DCE data is challenging since simultaneous intensity changes due to contrast agent and motion are a major obstacle for many conventional approaches. In this work we propose to overcome this problem by generating a virtual time series with reduced motion but conserved contrast-agent dynamic which is used as a template in an iterative registration process.

Methods
The proposed method of Virtual-Template-Registration (VTR) uses a registration of the motion-corrupted sequence onto a motion-free template in an iterative manner.

Virtual templates were generated by using independent-component-analysis (ICA) in order to remove the motion-related components. Registration was carried with free-form-deformation-registration. The registered time-series was then again used to generate a VT which resulted in a motion reduction in every step.

VTR was tested on clinical contrast-enhanced myocardial and renal perfusion data and on a synthetic kidney phantom that delivers a ground truth. Accuracy was evaluated by computing the RMSE to the ground truth. Motion displacements were evaluated over time before and after registration. Additionally, the mean intensity over a static ROI of the myocardium was evaluated for the cardiac perfusion data to show clinical relevance.

Results
The RMSE of the phantom was reduced by 73% compared to the motion-corrupted sequence. Absolute motion displacement range was reduced by 91% for the phantom, 60% for the cardiac-data and 67% for the renal-data, rendering an automatic evaluation of DCE-data possible, as mean intensity time curves over a static ROI further show.

Conclusion
VTR with the proposed ICA approach effectively compensates for motion in DCE-MRI data. It was successfully applied to clinical perfusion data and has the great potential of being a general approach for motion correction in DCE-MRI.

Acknowledgements
This work was funded by the Austrian Science Fund "SFB F3209-18" and by the funds of the Oesterreichische Nationalbank, Anniversary Fund (Grant Number 141223).
Influence of denoising techniques on the absolute CBF quantification of ASL perfusion data

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Introduction
The SNR in ASL images is critical low; therefore denoising is important. In previous studies denoising was performed separately in time and space. In the present work, we propose a total-generalized-variation (TGV) based approach that uses temporal and spatial information for denoising and further couples the denoising of control and label images. The performance of the proposed technique and its influence on the CBF quantification is investigated and compared with five common ASL denoising techniques.

Methods
For baseline evaluation synthetic CBF maps were generated based on anatomical MR data. Furthermore, in-vivo high-resolution pulsed ASL data were acquired on a 3T MR-system using PICORE-Q2TIPS single-shot EPI. CBF-maps of the acquired 500 control/label pairs served as pseudo-ground truth (Tscan=45min). As a general pre-processing, control/label images were motion corrected, detrended and outliers were removed. For the specific study, 50 control/label pairs (Tscan=4.5min) were simultaneously denoised in the spatio-temporal dimension with our variational method and compared to a selection of well-established spatial filters: Wavelet-based-Wiener, adaptive Wiener, Anisotropic Diffusion, BM3D and DT-CWT-ONLM. After denoising CBF-maps were computed using a single-compartment model. In order to evaluate the effects of filtering, the difference in the mean CBF between the ground-truth and the denoised CBF-map was calculated in both grey and white matter.

Results and Discussion
The results of our study showed that denoising in general improves the visual quality of the CBF-maps but introduced a bias in absolute CBF-quantification ranging from 11% to 4% in grey- and 10% to 5% in white matter. In both cases, synthetic and in-vivo data, the quantification of the CBF was most precise using the proposed TGV method.

Conclusion
The proposed approach exploiting the coupling of control-label pairs performed best and allows the acquisition of perfusion maps with a resolution similar to DSC-MRI within clinical acceptable scan times.

Acknowledgement
"SFB F3209-18"
Blood flow velocity measurements by Magnetic Particle Imaging

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Magnetic particle imaging is a new imaging modality in medicine. With a sampling rate of 46 volumes per second it is fast and free of ionizing radiation. The application of a magnetic tracer is mandatory. After intravenous injection its passage can be detected through the vascular system and its distribution in the body can be measured. We want to introduce analysis techniques applied to MPI data to track the propagation and to detect arrival times of the tracer material. First, we developed algorithms which fit a function to the signal time curve in each voxel. Next, we implemented a bolus tracking algorithm which analyses the movement of gravity of tracer distribution through 3D. To validate the algorithms, we build a flow phantom. We generated various flow velocities from 2 cm/s to 20 cm/s typical in a venous system of a mouse. Arrival time estimation analysis algorithm and those for bolus tracking were validated. This impact of velocity speeds on the accuracy was analysed. We found a good agreement with the predicted velocities in the phantom setting. In vivo measurements were performed in mice. Results analysed from MPI data were compared with those determined by magnetic resonance imaging. Here, a good agreement was found showing the feasibility to perform velocity measurements by MPI in vivo.
Development and Evaluation of a Web Based Platform to Assist the Segmentation of Medical Images Using Crowdsourcing

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Medical imaging plays a major role in today's medical diagnostics. The automatic segmentation of medical image data resulting in isolated anatomic structures is one of the most important research topics in this field. While it is rather easy for a physician to identify and classify different anatomical structures in an image, the same task can be massively more complex for a computer algorithm. In order to automatically segment image data, computer systems often have to be trained. This training depends on training data sets which in turn, must be segmented by hand. Unfortunately, the process of manually labelling a specific region in a volumetric data set is a very cumbersome task. Recently, several online crowdsourcing platforms which support the handling of human micro tasks have emerged. These platforms connect requesters having specific tasks, with crowd workers who can solve these tasks. The aim of this project is the development and evaluation of such a platform which allows the segmentation of volumetric medical image data with the help of crowd workers. The platform is implemented as a HTML5 single page web application, which runs in the web browser without the need of any additional installations or plug-ins. We evaluated the platform and the resulting segmentations in a user trial. The results showed, that the platform was well able to support the distributed segmentation process and that the segmentation of medical images within a browser is possible. The quality of the segmentations made by the crowd workers is quite promising, but strongly depends on the presentation and characterization of the tasks to the workers as well as on the domain knowledge of the workers.
Influence of Storage Technologies to the Overall Performance of Massively Parallel Cluster Computing Workflows in Intraoperative Thermal Imaging

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Intraoperative thermal imaging is an emerging technology to analyse cortical perfusion in neurosurgery. Neural activity monitoring represents one important application which can be achieved by exploiting neurovascular coupling. Increased metabolism caused by neural activity leads to local perfusion changes in eloquent areas of the brain that also correlate with weak temperature gradients. Knowledge about eloquent areas is important in case of tumour resections to support the surgeon’s decision about potential postoperative functional limitations. Inferring neural activity typically requires extensive experimental designs to increase statistical significance of the estimates. These experiments introduce a challenging amount of imaging data. In order to maximize the performance of the overall data processing workflow special attention has to be paid to the processing of a very large quantity of individual files. In this work, we propose the parallelization of a serial workflow by means of the MapReduce cluster computing paradigm. The approach allows massively parallel execution of the data processing workflow by restating it in terms of primitive operations. Apache Spark further enhances this paradigm by reducing disk accesses. This is especially favourable in case of large quantities of individual file input/output. Executing the data processing pipeline on a HPC cluster finally maximizes the throughput. We further quantify the scale-up of by an extensive evaluation scheme and found significant performance improvements compared to traditional approaches because of the inherent scalability. Another important influencing factor to the overall performance is the underlying storage technology. In contrast to traditional disk storage we furthermore evaluate the contribution of prevalent storage technologies, such as distributed storage or flash-based technologies. In summary, we reduced the overall runtime significantly by choosing the optimal storage technology for data I/O to enable maximum scalability of Apache Spark. Hence decreasing the delay of the intraoperative intervention by keeping the accuracy of the employed algorithms.
Intraoperative Hyperspectral Imaging extending Optical Imaging of stimulated active brain areas in neurosurgery – a feasibility study

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Following surgical planning based on MRI images, neurosurgeons intraoperatively need information about tumor localization and brain tissue functionality to define tumor resection borders. Electrophysiological measurements of brain activity are limited to the local spots of the used electrodes. In contrast, intraoperative optical imaging (IOI) identifies areas of increased metabolism caused by stimulation of specific brain functions. IOI uses a special hardware setup that analyzes selected wavelengths or broadband spectra (RGB) of the reflected light from the exposed cortex. Results after performing a stimulation protocol and complex image processing algorithms are two-dimensional navigated activity maps. Pseudocolored intraoperative calculated maps are characterizing the dynamics of relative intensity changes between rest and stimulation answer. They are visualized overlayed with a registered microscope image. IOI is already applicable in clinical routine use during neurosurgical interventions in combination with standard hardware equipment. Seeking for more information in reflected light images, acquired contact-free and without additional dye, the dynamics of wavelength information of the whole spectrum (500 ... 1000 nm) are acquired with hyperspectral imaging (HSI). The reflected light is decomposed into individual spectral components with high spatial and time resolution. A hyperspectral datacube includes spectral information for each pixel of the two-dimensional image from the exposed brain area. Using an adapted light source and a hyperspectral camera prototype at a separate surgical microscope in parallel to IOI, first examinations demonstrated the feasibility of HSI in neurosurgical operating room. Further work will focus on the light source, camera parameter optimization, motion and reflection disturbance reduction, and data analysis to decide, if the HSI method could be reduced to multispectral imaging for characterizing tumor and differentiating eloquent from non-eloquent brain areas. Comparing preoperative MRI, intraoperative IOI, and HSI images with intraoperative anatomical landmarks (and electrophysiological testing) intraoperative hyperspectral imaging seems to be a promising additional imaging option.
Evaluation of fluorescent cell image segmentation algorithms for overlapping cell on simulated fluorescent data sets with known ground truth

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Fluorescence microscopy of cell experiments is an important part in research on microbial effectors on target host cells. Nevertheless, manual delineation and analysis of the depicted cell in those images is time consuming and prone to errors leading to inter- and intra-observer variability. Hence, application of automated and semi-automated image segmentation algorithms is essential for high-throughput image analysis to ensure time efficiency and constant segmentation quality over a complete image set. Currently, expert based cell delineation is generally considered as the “gold standard” for the evaluation of such segmentation algorithms. But manual annotation and labelling of the image data is tedious and introduces errors (as mentioned above). Especially so, if fluorescent micrographs with complex image data depicting touching, overlapping or even overlaying cells are considered. Hence, in order to ensure an objective rating for such segmentation algorithms, we simulate realistic fluorescent image data sets including known ground truth, based on real fluorescent image data.

To enable the automated segmentation of touching or overlapping cells, an adaptive active contours approach is proposed. The approach is using a shape adaptive energy term calculated with an active shape model. Additionally, an intensity dependent interaction term between adjacent cells is introduced. The algorithm is evaluated on a series of five simulated micrograph data sets showing cells with increasing degree of overlap. These synthetic data sets are simulated based on image data depicting FDA stained protoplasts. The parameters of the segmentation algorithm are automatically adapted to the ground truth optimizing a metric combined by accuracy and Jaccard index.

The proposed algorithm produces a segmentation quality of 0.76 measured in Jaccard metric for isolated and touching cells to 0.61 for overlaying cells. The proposed algorithm is able to detect overlaps between adjacent cells and, thus, the segmentation quality is less dependent on the increasing degree of cell overlaps as for algorithms excluding overlaps.
Magnetic targeting of ferrofluids under liquid stream conditions for tumor therapy: simulation and experimental investigations

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Magnetic drug targeting (MDT) describes the selective targeting of therapeutics bound to magnetic nanoparticles (MNP) in a tissue or a region in the body, e.g. in a tumor, by magnetic fields. For an efficient tumor therapy with MDT, it is important that significant amounts of the drugs bound to MNP reach the tumor site.

In order to predict the accumulated amount of MNP in tumors, FEM simulations of the behavior of magnetic MNP in capillaries under the influence of a magnetic field were performed. The physical and chemical properties of the MNP as well as interactions between MNP were taken into account and the adsorption coefficient of the MNP at the capillary wall for different magnetic field configurations was calculated.

The simulation results were compared to experimental data taken from magnetic targeting investigations performed with self-synthesized MNP in a microfluidic setup which consisted of two micro-channels, several magnets and a light microscope with an integrated video camera. The analysis of the absorption coefficient of MNP in the microchannels was performed by image processing.

The highest predicted adsorption coefficient within one hour at the capillary wall was approx. 7 % of the MNP total amount flowing through the capillary. This value is much lower than the adsorption coefficient of approx. 54 % determined from experimental investigations. The big difference between these two values can be explained by the formation and accumulation of MNP agglomerates especially at the intersection of two microchannels which constitute more than one half of the total accumulated amount of MNP in the microchannels. This phenomenon must be considered for future simulations.
ID: O-PP-26

**Peptide-Modified Micelles and Liposomes: Carriers for Xenon Hyper-CEST MRI of Blood Brain Barrier Endothelial Cells**

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Selective imaging of pathological areas and targeted drug delivery are crucial for efficient diagnostics and therapy. Drug delivery to the brain is a particular challenge. We generated highly cationic lipopeptides that form micelles and bind to liposomes (1). Cargos, covalently bound or incorporated into such carriers are selectively transported into blood brain barrier endothelial cells (2,3). Basis for the selective uptake of the different systems is the activation of clathrin-mediated endocytosis, a process which is not addressed in other vessel endothelial cells.

Here we present the development of peptide-modified micellar and liposomal carriers for the selective transport of cryptophane-A (CrA) into human brain capillary endothelial cells. Chemical exchange saturation transfer with hyperpolarized xenon nuclei (Hyper-CEST) allows highly sensitive detection of supramolecular cages such as CrA in non-invasive Magnetic Resonance Imaging (MRI). Incorporation into liposomes distinctly reduced the toxicity of the hydrophobic CrA and a one nanomolar concentration generated sufficient contrast to distinguish between brain capillary and aortic endothelial cells. Covalent attachment did not influence the micelle characteristics and provided additional advantages as it results in high local cage concentration and allows more reliable quantification of the signal molecule. The peptide-modified carriers combine a high selectivity for human brain capillary endothelial cells with the great sensitivity of Xe Hyper-CEST MRI and might be a promising MRI tool.
Atomic magnetometers for magnetic susceptibility and magnetic particle imaging

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Superparamagnetic Iron Oxide Nanoparticles (SPIONs) are investigated in view of biomedical applications, such as markers, magnetic field enhancement agents, and drug carriers. Most of the SPION applications rely on or will greatly profit from a quantitative representation of their spatial distribution in biological fluids and tissue. SPION properties, in particular their response to DC and AC magnetic excitation, strongly depends on their size and environment. We show that atomic magnetometers (AM) can serve as sensitive detectors for recording the DC and low-frequency susceptibility of SPIONs in ranges that are not accessible to conventional pickup-coil-based instruments.

We will discuss in detail how AMs can be used for quantitative magnetic particle spectroscopy (MPS). The magnetization of SPIONs exposed to a harmonically oscillating field of several mT exhibits a characteristic anharmonicity, the spectrum of which is SPION size-distribution and environment specific. An MPS variant based on position-encoding by inhomogeneous fields yields an imaging modality called MPI (Magnetic Particle Imaging).

AM measure the time-dependent magnetic induction $B_{tot}$ produced by the SPION sample’s magnetization $M_{SPION}$. AM combine magnetic resonance with (laser) optical preparation/detection in a vapour of spin-polarized alkali atoms. In the chosen mode of operation the intensity of the laser beam transmitted by the vapour becomes modulated at the Larmor frequency that is proportional to the $|B_{tot}(t)| = |B_0 + B_{SPION}(t)|$. Phase-sensitive demodulation allows the extraction of the signal of interest $M_{SPION} B_{SPION}$.

The performance of our AM-based MPS device in terms of harmonics detection is comparable to the one achieved by commercial instruments, while operating in quasi-DC to a frequencies of a few tens of Hz. We are currently developing an AM-based MPI scanner and will report on its status.
Magnetic Characterization of Phantom Materials by Magnetic Particle Spectroscopy

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Magnetic nanoparticles (MNP) are used in imaging modalities either to enhance the contrast as in magnetic resonance tomography or as direct probes as in magnetic particle imaging. To assess the performance of these imaging modalities sophisticated phantoms with defined MNP distributions have to be designed. All phantom materials should be inert, should not contain any magnetic impurities and should not exhibit interactions with MNP.

To this end we investigated different 3D printing polymers and tubing materials using magnetic particle spectroscopy (MPS). MPS is capable to quantify magnetic impurities of the phantom materials and the amount of MNP that may adhere to the polymers and tubing material. We investigated the adhesion behavior by filling four different MNP suspensions (Fluidmag-D, Resovist, Endorem, Feraheme) into different 3D printed small containers (E-Shell 200, E-Shell 600, R05 Gray, R05) and tubing materials (Silicon, FEP, Tygon, PTFE, PVC) with an inner contact surface of 25 mm². After 5 minutes the MNP were removed and the material probes were cleaned with ultra-pure water.

The measured MPS signals ($B_{exc}=25$ mT, $f_{exc}=25$ kHz) were used to quantify the adhered MNP amount by referencing to samples with known MNP amount. The MNP adhesion significantly varied for polymer materials. Silicon has one order of magnitude higher adhesion than PTFE. Of the MNP, Fluidmag-D shows strongest adhesion to the tested materials with an eight times higher adhesion to R05 and four times higher to PTFE as compared with Resovist.

To conclude, MPS is ideally suitable to assist the development of phantoms by rapid and sensitive magnetic material characterization using small alliqrt samples.
Magnetic Nanoparticle-Gel Materials for Development of Long-Term Stable Magnetic Particle Imaging Phantoms

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Magnetic Particle Imaging (MPI) is a promising approach to determine the spatial distribution of magnetic nanoparticles (MNP) within tissue. To evaluate the performance of existing MPI-scanners, dedicated phantoms with predefined MNP distributions are essential.

Prerequisite for the development of such phantoms is the establishment of suitable MNP-matrix combinations. They should enable homogeneous MNP distributions at defined concentrations combined with immobilization of the MNP within the matrix to guarantee long-term stability of magnetic behavior and high mechanical stability of the matrix material. Therefore, two different gel types, water based biopolymers (e.g. agarose) and synthetic polymers (e.g. silicones), were used as matrix materials. Both show similar imaging behavior in MRI and MPI compared to body tissue. Aqueous suspensions of MNP coated with functionalized dextranes were embedded into biopolymers, and organic fluids (e.g. dodecane) with oleic acid coated MNP into synthetic polymers, respectively.

The obtained MNP-matrix combinations were tested for their mechanical stability. The homogeneity of MNP distribution was investigated with a microscope and the immobilization of the MNP within the matrix was measured with vibrating sample magnetometry. Appropriate MNP-matrix combinations were used to manufacture measurement objects of different shape (spheres, cylinders, cubes) and different size (5, 10, 20 mm) embedded in a phantom matrix with a geometry of a cylinder with D = 50 mm and H = 60 mm. Those phantoms were evaluated for their suitability to simulate MNP loaded areas within a nonmagnetic matrix by means of MRI (Bruker Icon) and MPI (Bruker BioSpin preclinical MPI-scanner).

In summary, we found suitable combinations of coated magnetic nanoparticles and matrix materials for the build-up of long-term stable MPI phantoms, which guarantee a fixation of the MNP within the matrix without agglomeration of the particles. Several strategies for preparation of measurement phantoms were tested and will be discussed in our presentation.

This work is supported by Deutsche Forschungsgemeinschaft (FKZ: DU 1293/6-1 and TR408/9-1).
Fast Assessment of Magnetic Nanoparticle Tracers applying a Preclinical MPI scanner

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Magnetic Particle Imaging (MPI) is a novel biomedical imaging modality capable to quantify magnetic nanoparticles (MNP) with excellent temporal and spatial resolution. Besides the development of MPI scanner systems and image reconstruction, MNP properties are of vital importance for MPI image quality. Magnetic Particle Spectroscopy (MPS) has been proven a valuable tool to estimate the signals of a given tracer that can be expected in MPI. MPS constitutes the zero dimensional counterpart of MPI as it is based on the same physical principle to detect the non-linear magnetization response of MNP.

In order to allow a direct measure of the MPI performance of MNP in a given MPI scanner, we developed a more straightforward procedure for tracer evaluation using the preclinical Bruker MPI system. Therefore, the peculiarities of the signal spectra obtained with MPS (Bruker MPS-3) and the preclinical MPI scanner (Bruker 25/20), both operating at the same frequency, of structurally different MNP (Fluidmag, Chemicell GmbH; Resovist®, Bayer HealthCare; multi-core MNP, Charité) were investigated and compared. Whereas, MPS uses an uniaxial excitation to detect spectral magnetic signals (down to $5 \cdot 10^{-12} \text{Am}^2$) of a tracer sample, the preclinical MPI scanner moves the so-called Field-Free-Point through the sample volume along a 3D Lissajous trajectory (gradient fields: 1.25, 1.25 and 2.50 T/m). The sensitivity of the coils and of the electronics are currently unknown, but similar on the scanner of the same series.

To correlate MPI and MPS signals, we applied the harmonic number at which the MNP signal reached the level of background signal. We found correlations between the spectra generated by both devices for different tracer types, concentration and volumes. Using the MPI spectra allowed for direct assessment of MPI performance of the different MNP types circumventing the time consuming system function acquisition.